REMARKS

Claims 1-4, 6, 7, 9-11, 13, 25-28, 30, 31, 33-35, 37, 55, 58 and 59 are pending in the case. Claims 14-24, 38-54, 56, 57, and 60-63 are herein withdrawn. Claim 55 is objected to under 37 C.F.R. § 1.75(c) as being in improper form. Claims 1-13, 25-37, 55, 58 and 59 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Wheelhouse *et al.* (U.S. Patent No. 6,087,493; hereafter "*Wheelhouse*") in view of Argyris *et al.* (1999, *J. Biol. Chem.* 274(3):1549-1556; hereafter *"Argyris"*). Claims 1, 25, 55 and 58 are herein amended. Claims 5, 8, 12, 29, 32 and 36 are herein cancelled. No new matter has been introduced.

Reconsideration of the present application in view of the foregoing amendments and the remarks below is respectfully requested.

Claim Objection

Claim 55 is objected to under 37 C.F.R. § 1.75(c) as being in improper form because it depends from a non-elected Group IV claim.

Claim 55 is herein amended to depend from claim 25, which belongs to an elected invention of Group I.

Accordingly, Applicants respectfully request that the objection of claim 55 under 37 C.F.R. § 1.75(c) be withdrawn.

Claim Rejections under 35 U.S.C. § 103

Claims 1-13, 25-37, 55 and 58-59 are rejected under 35 U.S.C. § 103(a) as being unpatentable over *Wheelhouse* in view of *Argyris*.

Specifically, the Office Action states that *Wheelhouse* teaches modulating tumor proliferation and mortality in animal models using a metal porphyrin, including gold porphyrin, and discloses that a wide range of pyridyl and quinolyl-aldehyde substituted porphyrins are available using combinatorial syntheses. Further, the Office Action states that *Argyris* teaches "six membered heteroaryls which represents substituents of R(1, 4, 7 and 10)" and that one skilled in the art "would have been motivated to select the claimed invention with the expectation that substitution of the R(1-12) would not significantly alter the analogous properties of the compound of the reference due to close structural similarity of the compounds and based on the fact that the general substituent is taught in the prior art".

Applicants respectfully traverse the rejection.

Wheelhouse discloses cationic porphyrins that ***inhibit telomerase activities*** by stabilizing or disrupting the G-quadruplex structure of the telomeric DNA and thereby modulating tumor proliferation and mortality in animal models (*see* ABSTRACT and col. 2, lines 29-41). *Wheelhouse* particularly focuses on porphyrins that are meso-substituted with substituted pyridines and quinolines, such as 5,10,15,20-tetra-(N-methyl-4-pyridyl)porphyrins (TMPyP4), which have appropriate sizes to stack with the G-tetrads of quadruplex DNA and disrupts the helical structure of the adjacent DNA by intercalation. *Wheelhouse* does not disclose a method that directly induces apoptosis in cancer cells. Further, *Wheelhouse* does ***not*** disclose anything about a method for inhibiting reverse transciptase (RT) of human immunodeficiency virus type 1 (HIV-1).

Argyris discloses that heme and zinc protoporphyrin inhibit human immunodeficiency virus type 1 (HIV-1) and type 2 (HIV-2) RTs by binding to the highly conserved region 398-407 of the viral RTs. *Argyris* does ***not*** disclose anything about anti-tumor activity of heme and zinc protoporphyrin. Furthermore, on the contrary to the Examiner's assertion, *Argyris* does ***not*** disclose anything about "six membered

heteroaryls which represent substituents of R(1, 4, 7 and 10)". As such, there is no suggestion or motivation for one skilled in the art in either of these two references to combine with each other to come up with the methods recited in the present claims.

In addition, Applicants strongly disagree with the Examiner's statement that by combining *Wheelhouse* and *Argyris* "an ordinary skill in the art would have the reasonable expectation of success" with regard to anti-tumor activities.

First of all, even with regard to telomerase inhibition activities (as opposed to anti-tumor activities), there is a great variation in % inhibition among different metals as well as different substituents of porphyrins, ranging from 2% to 88% inhibition (see Table 4 at col. 45 of *Wheelhouse*). Among the metals tested, AuIII porphyrin exhibited only 23% telomerase inhibition, compared to 88% inhibition with H2 or ZnII porphyrin. Thus, *Wheelhouse* actually teaches away from the methods of the present invention that uses a composition comprising a gold(III) complex of the formula recited in present claims 1, 25 and 58. Furthermore, Tables 5-15 of *Wheelhouse* indicate that porphyrins with various substituents also have considerable variations in telomerase inhibitory activities, some of them being totally inactive (*see*, for example, B8 and B28 in Table 5, B26 in Table 7, H10, H16, H28, H29 and H32 in Table 15).

Thus, there is no reasonable expectation of success in *Wheelhouse* that any substituents for R1-R12 would have equally effective anti-telomerase activities, let alone effective anti-tumor activities inducing apoptosis in cancer cells. And Argyris, which does not teach or even suggest anything about anti-tumor activities, cannot cure this defect.

In contrast, the present inventor has demonstrated that the use of gold (III) porphyrins achieves acute cytotoxicity and, hence, anti-tumor activities, and that different substituents ***do*** make differences in their anti-tumor activities. In particular, the

present inventor has shown that the gold(III) porphyrins, ***without pyridyl or quinolyl aldehydes***, exhibit acute cytotoxicity toward cancer cells during 48-hour incubation. The present inventor has recognized that, although gold(III) is well known to be cytotoxic, most gold(III) compounds are unstable with regard to reduction to gold(I) and demetallation under physiological condition. Thus, the present inventor reasoned that stabilization of gold(III) using porphyrin ligand and carrying the metal to its cellular target is the key to achieve high toxicity. Indeed, this was exactly the case. The porphyrin ligand stabilizes gold(III) from demetallation and leads to the reduction of gold(III) at a very negative potential. As shown in Table 4a at page 40 of the present specification, the gold(III) complex of tetraphenylporphyrin ("1a") ($[Au^{III}(TPP)]Cl$, in which the porphyrin ligand is the most common type of porphyrin ligand to date) exhibited high cytotoxicity with IC_{50} value (*i.e.*, a concentration required to kill 50% cancer cells) of ~$1x10^{-7}$M. In contrast, a pyridyl-containing gold(III) porphyrin ("1j") ($[Au^{III}(TMPyP)]Cl_5$), which are shown to inhibit telomerase by *Wheelhouse*, was indeed found ***no acute cytotoxicity*** (IC_{50} > $5x10^{-5}$ M, which is about 500 times less potent than $[Au^{III}(TPP)]Cl$).

Furthermore, based on the viscosity evaluation and gel mobility shift assay, the present inventor has also shown that the claimed gold(III) porphyrins (except for $[Au^{III}(TMPyP)]Cl_5$) do ***not*** bind DNA via intercalation (*see* paragraphs [00188] through [00190] at page 46 of the present specification). It should be noted that intercalation (*i.e.*, π-stacking in between DNA base pairs) is the essential DNA binding mode for *Wheelhouse*'s disclosed compounds to stabilize G-quaduplex formations. In fact, using $[Au^{III}(TPP)]Cl$ (hereafter "gold 1a") as model, the molecular mechanisms of the cytotoxicity induced by the gold(III) porphyrins of the present invention have been shown to involve the binding of the compound to mitochondrial DNA, induction of reactive oxygen species (*see* "Gold(III) Porphyrin 1a Induced Apoptosis by Mitochondrial Death Pathways Related to Reactive Oxygen Species", 2005, *Cancer Res* 65(24):11553-11564 by Ying Wang *et al.*, a copy of which is attached hereto for the

Examiner's reference) and the induction of apoptosis (*see* paragraph [00191] at page 46 through paragraph [00196] at page 48, of the present specification).

The present inventor has clearly demonstrated that ***neither*** the gold(III) ion itself ***nor*** any metal-free porphyrin alone would induce as higher as cytotoxic activities compared to that of the gold(III) porphyrins. For example, gold 1a of the present invention exhibited potent cytotoxicity toward different types of cancer cells (*see* Table 4a, entry 1), while the metal-free porphyrin (H_2TPP) and its zinc derivative [Zn^{II}(TPP)] (Table 4a, entry 14) are at least about 70-fold (IC_{50}>50 μM) less potent than gold 1a. Yet, the porphyrin ligand is also essential for the gold 1a's anticancer activity, since a gold(III) salt ($K[Au^{III}Cl_4]$) (Table 4a, entry 12) was about 10-100 times less cytotoxic.

Thus, simply following *Wheelhouse* alone or combining it with *Argyris* by one with ordinary skill in the art to synthesize new porphyrins would not result in the present invention claimed in claims 1-13, 58 and 59, in terms of the cytotoxicity, DNA binding activities, and the cell death mechanism.

Likewise, although *Argyris* discloses that zinc and iron porphyrin (*i.e.*, protoporphyrin and hematoporphyrin) inhibit HIV RTs, it, alone or even in combination with *Wheelhouse* (the latter does not teach anything about a method for inhibiting HIV-1 RT anyway), does not teach or even suggest that the gold(III) complex as claimed in the present application would exhibit surprising degree of anti-HIV-1 RT. Furthermore, the present application discloses the evidence that not all kinds of porphyrin would have significant anti-HIV-1 RT activities, about which *Argyris* is totally silent. For example, the present application has demonstrated that $[Au^{III}(TMPyP)]Cl_5$ ("1j") and $Na_4[Au^{III}(TPPS)]Cl$ ("1k") exhibit over 73% and 71% inhibition, respectively, at 6 μm level of the RT activity, whereas the metal-free porphyrins, $[H_2TMPyP]^{4+}$ and $[H_2TPPS]^{4-}$, show less than 30% inhibition (*see* Fig. 14). Thus, the Examiner's statement that the

present claims differ only in the sense that the prior art does not specifically teach all the substituents of R(1-12) is in error.

Thus, claims 25-37 and 55 are not obvious over *Wheelhouse* and *Argyris*, each alone or in combination.

Nevertheless, claims 1, 25, 55 and 58 are herein amended and claims 5, 8, 12, 29, 32 and 36 are herein cancelled, to solely accelerate the prosecution of the present application.

Accordingly, Applicant respectfully requests that the claim rejections under 35 U.S.C. § 103(a) as being unpatentable over *Wheelhouse* in view of *Argyris* be withdrawn.

No fee is believed to be due for this submission. Should any fee(s) be required, please charge such fee(s) to Deposit Account No. 50-2215.

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Respectfully submitted,

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Attachment: "Gold(III) Porphyrin 1a Induced Apoptosis by Mitochondrial Death Pathways Related to Reactive Oxygen Species", 2005, *Cancer Res* 65(24):11553-11564.